

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

75-837

Generic Name: Floxuridine for Injection USP, 500 mg/ vial

Sponsor: American Pharmaceutical Partners, Inc.

Approval Date: February 22, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-837

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-837

APPROVAL LETTER

ANDA 75-837

FEB 22 2001

American Pharmaceutical Partners, Inc.
Attention: Tom Stothoff
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Sir:

This is in reference to your abbreviated new drug application dated March 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Floxuridine for Injection USP, 500 mg/vial.

Reference is also made to your amendment dated January 15, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Floxuridine for Injection USP, 500 mg/vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (FUDR[®] Injection, 500 mg/vial, of Hoffmann La Roche Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

JSJ
Gary Buehler 2/22/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-837

Final Printed Labeling

The acute intravenous toxicity of floxuridine is as follows:

Species	LD ₅₀ (mg/kg ± S.E.)
Mouse	880 ± 51
Rat	670 ± 73
Rabbit	94 ± 19.6
Dog	157 ± 46

DOSAGE AND ADMINISTRATION:

Each vial must be reconstituted with 5 mL of sterile water for injection to yield a solution containing approximately 100 mg of floxuridine/mL. The calculated daily dose(s) of the drug is then diluted with 5% dextrose or 0.9% sodium chloride injection to a volume appropriate for the infusion apparatus to be used. The administration of floxuridine is best achieved with the use of an appropriate pump to overcome pressure in large arteries and to ensure a uniform rate of infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The recommended therapeutic dosage schedule of floxuridine by continuous arterial infusion is 0.1 to 0.6 mg/kg/day. The higher dosage ranges (0.4 to 0.6 mg) are usually employed for hepatic artery infusion because the liver metabolizes the drug, thus reducing the potential for systemic toxicity. Therapy can be given until adverse reactions appear. (See **PRECAUTIONS**). When these side effects have subsided, therapy may be resumed. The patients should be maintained on therapy as long as response to floxuridine continues.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.^{1,7} There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

Product No.	NDC No.	Description
104507	63323-145-07	Floxuridine for Injection, USP 500 mg floxuridine powder in a 5 mL vial, packaged individually. This is to be reconstituted with 5 mL sterile water for injection.

Vial stoppers do not contain natural rubber latex.

The sterile powder should be stored at 15° to 30°C (59° to 86°F). Reconstituted vials should be stored under refrigeration 2° to 8°C (36° to 46°F) for not more than 2 weeks.

REFERENCES:

1. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC, US Government Printing Office NIH publication 83-2621.
2. AMA Council Report. Guidelines for handling parenteral antineoplastics. *JAMA*. Mar 15, 1985; 253:1590-1592.
3. National Study Commission on Cytotoxic Exposure: Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Aust*. Apr 30, 1983; 1:426-428.
5. Jones, RB, Frank R, Mass T: Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA*. Sept-Oct, 1983; 33:258-263.
6. ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. *AM J Hosp Pharm*. Jan, 1985; 42:131-137.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm*. 1986; 43:1193-1204.

APP AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

45914
Issued: October 2000

APP AMERICAN PHARMACEUTICAL PARTNERS, INC.

45914/Issued: October 2000

FLOXURIDINE

FOR INJECTION, USP

FOR INTRA-ARTERIAL INFUSION ONLY

WARNING

It is recommended that Floxuridine for Injection, USP be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and intra-arterial drug therapy and is well versed in the use of potent antimetabolites.

Because of the possibility of severe toxic reactions, all patients should be hospitalized for initiation of the first course of therapy.

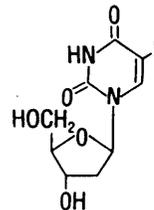
DESCRIPTION:

Floxuridine for Injection, USP, an antineoplastic antimetabolite, is available as a sterile, non-pyrogenic, lyophilized powder for reconstitution. Each vial contains 500 mg of floxuridine which is to be reconstituted with 5 mL of sterile water for injection. An appropriate amount of reconstituted solution is then diluted with a parenteral solution for intra-arterial infusion (see **DOSAGE AND ADMINISTRATION**).

Floxuridine is a fluorinated pyrimidine. Chemically, floxuridine is 2'-deoxy-5-fluorouridine. It is a white to off-white odorless solid which is freely soluble in water.

The 2% aqueous solution has a pH of between 4.0 and 5.5.

The structural formula is:



C₉H₁₁FN₂O₅

M.W. 246.19

CLINICAL PHARMACOLOGY:

When floxuridine is given by rapid intra-arterial injection it is apparently rapidly catabolized to 5-fluorouracil. Thus, rapid injection of floxuridine produces the same toxic and antimetabolic effects as does 5-fluorouracil. The primary effect is to interfere with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibit the formation of ribonucleic acid (RNA). However, when floxuridine is given by continuous intra-arterial infusion its direct anabolism to floxuridine-monophosphate is enhanced, thus increasing the inhibition of DNA.

Floxuridine is metabolized in the liver. The drug is excreted intact and as urea, fluorouracil, α-fluoro-β-ureidopropionic acid, dihydrofluorouracil, α-fluoro-β-guanidopropionic acid and α-fluoro-β-alanine in the urine; it is also excreted as respiratory carbon dioxide. Pharmacokinetic data on intra-arterial infusion of floxuridine are not available.

INDICATIONS AND USAGE:

Floxuridine for Injection, USP is effective in the palliative management of gastrointestinal adenocarcinoma metastatic to the liver, when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means. Patients with known disease extending beyond an area capable of infusion via a single artery should, except in unusual circumstances, be considered for systemic therapy with other chemotherapeutic agents.

CONTRAINDICATIONS:

Floxuridine therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections.

WARNINGS:

BECAUSE OF THE POSSIBILITY OF SEVERE TOXIC REACTIONS, ALL PATIENTS SHOULD BE HOSPITALIZED FOR THE FIRST COURSE OF THERAPY.

Floxuridine should be used with extreme caution in poor risk patients with impaired

hepatic or renal function or a history of high-dose pelvic irradiation or previous use of alkylating agents. The drug is not intended as an adjuvant to surgery.

Floxuridine may cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates; skeletal defects; and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 4.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with floxuridine in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Combination Therapy

Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of floxuridine.

PRECAUTIONS:

General

Floxuridine is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of floxuridine despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

- Myocardial ischemia
- Stomatitis or esophagopharyngitis, at the first visible sign
- Leukopenia (WBC under 3500) or a rapidly falling white blood count
- Vomiting, intractable
- Diarrhea, frequent bowel movements or watery stools
- Gastrointestinal ulceration and bleeding
- Thrombocytopenia (platelets under 100,000)
- Hemorrhage from any site

Information for Patients

Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests

Careful monitoring of the white blood count and platelet count is recommended.

Drug Interactions

See WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of floxuridine have not been conducted. On the basis of the available data, no evaluation can be made of the carcinogenic risk of floxuridine to humans.

Mutagenesis

Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by floxuridine, but the relationship between oncogenicity and mutagenicity is not clear. Floxuridine has also been shown to be mutagenic in human leukocytes *in vitro* and in the *Drosophila* test system. In addition, 5-fluorouracil, to which floxuridine is catabolized when given by intra-arterial injection, has been shown to be mutagenic in *in vitro* tests.

Impairment of Fertility

The effects of floxuridine on fertility and general reproductive performance have not been studied in animals. However, because floxuridine is catabolized to 5-fluorouracil, it should be noted that 5-fluorouracil has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats at doses of 125 or 250 mg/kg, administered intraperitoneally.

Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. In female rats, fluorouracil, administered intraperitoneally at doses of 25 or 50 mg/kg during the preovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of preimplantation lethality and

induced chromosomal anomalies in these embryos. Compounds such as floxuridine, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Pregnancy

Teratogenic Effects: Pregnancy category D.

See WARNINGS. Floxuridine has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 3.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with floxuridine in pregnant women. While there is no evidence of teratogenicity in humans due to floxuridine, it should be kept in mind that other drugs which inhibit DNA synthesis (eg, methotrexate and aminopterin) have been reported to be teratogenic in humans. Floxuridine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Floxuridine has not been studied in animals for its effects on peri- and postnatal development. However, compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers

It is not known whether floxuridine is excreted in human milk. Because floxuridine inhibits DNA and RNA synthesis, mothers should not nurse while receiving this drug.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Adverse reactions to the arterial infusion of floxuridine are generally related to the procedural complications of regional arterial infusion.

The more common adverse reactions to the drug are nausea, vomiting, diarrhea, enteritis, stomatitis and localized erythema. The more common laboratory abnormalities are anemia, leukopenia, thrombocytopenia and elevations of alkaline phosphatase, serum transaminase, serum bilirubin and lactic dehydrogenase.

Other adverse reactions are:

Gastrointestinal: duodenal ulcer, duodenitis, gastritis, bleeding, gastroenteritis, glossitis, pharyngitis, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis, as well as acalculous cholecystitis.

Dermatologic: alopecia, dermatitis, nonspecific skin toxicity, rash.

Cardiovascular: myocardial ischemia.

Miscellaneous Clinical Reactions: fever, lethargy, malaise, weakness.

Laboratory Abnormalities: BSP, prothrombin, total proteins, sedimentation rate and thrombopenia.

Procedural Complications of Regional Arterial Infusion: arterial aneurysm; arterial ischemia; arterial thrombosis; embolism; fibromyositis; thrombophlebitis; hepatic necrosis; abscesses; infection at catheter site; bleeding at catheter site; catheter blocked, displaced or leaking.

The following adverse reactions have not been reported with floxuridine but have been noted following the administration of 5-fluorouracil. While the possibility of these occurring following floxuridine therapy is remote because of its regional administration, one should be alert for these reactions following the administration of floxuridine because of the pharmacological similarity of these two drugs: pancytopenia, agranulocytosis, myocardial ischemia, angina, anaphylaxis, generalized allergic reactions, acute cerebellar syndrome, nystagmus, headache, dry skin, fissuring, photosensitivity, pruritic maculopapular rash, increased pigmentation of the skin, vein pigmentation, lacrimal duct stenosis, visual changes, lacrimation, photophobia, disorientation, confusion, euphoria, epistaxis and nail changes, including loss of nails.

OVERDOSAGE:

The possibility of overdosage with floxuridine is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdosage of floxuridine should be monitored hematologically for at least 4 weeks. Should abnormalities appear, appropriate therapy should be utilized.

ANDA 75-837
Floxuridine for Injection, USP

Amendment – Response to
10/6/00 Deficiency Letter

NDC 63323-145-07 104507
[REDACTED]
FOR INJECTION, USP
[REDACTED]
Powder for reconstitution of
parenteral solutions.
**FOR INTRA-ARTERIAL
USE ONLY**
Rx only

Each vial contains: 500 mg of
floxuridine in dry powder form
for reconstitution of parenteral
solutions of floxuridine for
injection, USP.
For reconstitution, dosage, and
prescribing information, read
insert.
Store powder at 15° to 30°C (59°
to 86°F). Store reconstituted
solutions under refrigeration at 2°
to 8°C (36° to 46°F) for not more than
2 weeks.
Vial stoppers do not contain
natural rubber latex.

APP
Los Angeles, CA
402000

RECEIVED
FEB 22 2001

Vial Label

POWDER
[REDACTED]
FOR INJECTION, USP
[REDACTED]

Each vial contains: 500 mg
of floxuridine in dry powder
form for reconstitution
of parenteral solutions of
Floxuridine for Injection,
USP.
For reconstitution, dosage,
and prescribing information,
read insert.
Vial stoppers do not contain
natural rubber latex.

**STORE POWDER AT 15°
TO 30°C (59° TO 86°F).**
Store reconstituted vial
under refrigeration at 2°
to 8°C (36° to 46°F) for
not more than 2 weeks.

NDC 63323-145-07 104507
[REDACTED]
FOR INJECTION, USP
[REDACTED]
Powder for reconstitution
of parenteral solutions.
**FOR INTRA-ARTERIAL
USE ONLY**
Rx only



APP
Los Angeles, CA 90024

APP

APP

Carton

American Pharmaceutical Partners, Inc.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-837

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.1

2. ANDA # 75-837

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc (APP)
2045 North Cornell Avenue
Melrose Park, IL 60160

4. BASIS OF SUBMISSION

The listed drug product is FUDR® (Floxuridine for Injection USP), 500 mg/vial in 5 mL vial manufactured by Roche Laboratories, Inc. APP has submitted Patent Certification on page 009. APP certifies that, in their opinion and to the best of their knowledge, patents information has not been filed with the FDA with respect to Floxuridine for Injection USP for which APP seeks marketing clearance. Furthermore, APP certifies that there are no exclusivity periods in effect with respect the Floxuridine for Injection USP drug product that has been referenced by APP in this ANDA.

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product. Floxuridine for Injection USP is a sterile lyophilized powder for reconstitution containing 500 mg/vial floxuridine USP which is intended for intra-arterial infusion.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Floxuridine for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 3-31-00

NC: 4-12-00

Amendment: 8-25-00

FDA:

Accepted for filing: 4-4-00 (Acknowledgment letter: 5-3-00)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC
Rx

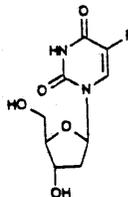
12. RELATED IND/NDA/DMF(s)
ANDA 75-387 Approved ANDA for the drug product
DMF _____
DMF _____
DMF _____
DMF _____
DMF _____

13. DOSAGE FORM 14. POTENCY
Injection 500 mg/Vial

15. CHEMICAL NAME AND STRUCTURE
Name: Floxuridine, 2'-Deoxy-5-fluorouridine, C₉H₁₁NF₂O₅.

M.W: _____

CAS NO. [50-91-9].



16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. GENERAL COMMENTS:

1. DMF _____ of Floxuridine USP is inadequate per review conducted by this reviewer dated 9-19-00.
2. Adequate information is provided for the manufacturing facility and outside testing facilities
3. Both Floxuridine and Floxuridine for Injection are USP materials.
4. APP specifications for Floxuridine are based on USP 24 and in-house.
5. Adequate information is submitted regarding executed batch and the intended production size batch. Microbiologist's review is pending.
6. Bio waiver - acceptable.
7. EER for all the facilities is pending.

B. COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments included in the section nos. 22, 25, 28, 29, and 33.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with MINOR amendment is being faxed to the firm including all the deficiencies identified in this review.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

9-20-00

Revised on 9-25-00 to include Mike Smela's comments.

APPEARS THIS WAY
ON ORIGINAL

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secret and/or

confidential

commercial

information

Chemistry Closed

1. CHEMISTRY REVIEW NO.2

2. ANDA # 75-837

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc (APP)
2045 North Cornell Avenue
Melrose Park, IL 60160

4. BASIS OF SUBMISSION
The listed drug product is FUDR® (Floxuridine for Injection USP),
500 mg/vial in 5 mL vial manufactured by Roche Laboratories, Inc.

APP has submitted Patent Certification on page 009.

APP certifies that, in their opinion and to the best of their knowledge, patents information has not been filed with the FDA with respect to Floxuridine for Injection USP for which APP seeks marketing clearance.

APP certifies that there are no exclusivity periods in effect with respect the Floxuridine for Injection USP drug product that has been referenced by APP in this ANDA.

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

Floxuridine for Injection USP is a sterile lyophilized powder for reconstitution containing 500 mg/vial Floxuridine USP which is intended for intra-arterial infusion.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Floxuridine for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 3-31-00
NC: 4-12-00
Amendment: 8-25-00

- Minor Amendment: 11-4-00 (Response to 10-6-00 NA letter)

FDA:

Accepted for filing: 4-4-00 (Acknowledgment letter: 5-3-00)
NA letter: 10-6-00

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

ANDA 75-387 Approved ANDA for the drug product

DMF _____

DMF _____

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM

Injection

14. POTENCY

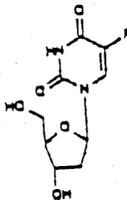
500 mg/Vial

15. CHEMICAL NAME AND STRUCTURE

Name: Floxuridine, 2'-Deoxy-5-fluorouridine, C₉H₁₁NF₂O₅.

M.W: _____

CAS NO. [50-91-9].



16. RECORDS AND REPORTS

N/A

17. COMMENTS

1. DMF _____ - the _____ of Floxuridine USP is adequate per review conducted by this reviewer dated 11-20-00.
2. Both Floxuridine and Floxuridine for Injection are USP materials.
3. Microbiologist's review is pending.
4. Bio waiver - acceptable.
5. EER for all the facilities is pending.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry Closed.

EER is pending.
Micro review is pending.

19. REVIEWER: DATE COMPLETED:
Mujahid L. Shaikh 11-20-00
Edited on 11-29-00

cc: AND 75-837
DUP File
Division File
Field Copy
Reading File

Endorsements:

HFD-625/M.Shaikh
HFD-625/M.Smela/

V:\firmsam\app\ltrs&rev\75837.RV2
F/T by:

IS/ 11/29/00
IS/ 11/29/00

APPEARS THIS WAY
ON ORIGINAL

Redacted

13

pages of trade

secret and/or

confidential

commercial

information

1. CHEMISTRY REVIEW NO.3

2. ANDA # 75-837

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc (APP)
2045 North Cornell Avenue
Melrose Park, IL 60160

4. BASIS OF SUBMISSION

The listed drug product is FUDR® (Floxuridine for Injection USP),
500 mg/vial in 5 mL vial manufactured by Roche Laboratories, Inc.

APP has submitted Patent Certification on page 009.

APP certifies that, in their opinion and to the best of their
knowledge, patents information has not been filed with the FDA with
respect to Floxuridine for Injection USP for which APP seeks
marketing clearance.

APP certifies that there are no exclusivity periods in effect with
respect the Floxuridine for Injection USP drug product that has been
referenced by APP in this ANDA.

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active ingredient, route of administration, dosage form, strength
and labeling is same as listed drug product.

Floxuridine for Injection USP is a sterile lyophilized powder for
reconstitution containing 500 mg/vial Floxuridine USP which is
intended for intra-arterial infusion.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Floxuridine for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 3-31-00

NC: 4-12-00

Amendment: 8-25-00

Minor Amendment :11-4-00 (Response to 10-6-00 NA letter)

* Fax Amendment: 1-15-01 (Response to 12-21-00 NA letter)

FDA:

Accepted for filing: 4-4-00 (Acknowledgment letter: 5-3-00)

NA letter: 10-6-00

NA letter: 12-21-00

10. PHARMACOLOGICAL CATEGORY
Antineoplastic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF _____

DMF _____

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM
Injection

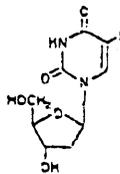
14. POTENCY
500 mg/Vial

15. CHEMICAL NAME AND STRUCTURE

Name: Floxuridine, 2'-Deoxy-5-fluorouridine, C₉H₁₁NF₂O₅.

M.W. _____

CAS NO. [50-91-9].



16. RECORDS AND REPORTS
N/A

17. COMMENTS

1. DMF _____

adequate per review conducted by this reviewer dated 11-20-00.

2. Both Floxuridine and Floxuridine for Injection are USP materials.

3. Microbiologist's review became acceptable.

4. Bio waiver - acceptable.

5. EER for all the facilities is pending.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

EER is pending.

19. REVIEWER: DATE COMPLETED:
Mujahid L. Shaikh 1-26-01

cc: AND 75-837
DUP File
Division File
Field Copy
Reading File

Endorsements:

HFD-625/M.Shaikh/1/26/01
HFD-625/M.Smela/1/26/01

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F/T by: DJ 1/26/01

ISI

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1/30/01

APPEARS THIS WAY
ON ORIGINAL

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confidential

commercial

information

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

75-837

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #1
December 5, 2000

- A. 1. ANDA 75-837
APPLICANT: American Pharmaceutical Partners, Inc.
2. PRODUCT NAME: Floxuridine for Injection, USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg/vial; Intra arterial infusion.
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: March 31, 2000
Subject of this Review (Received April 4, 2000)
2. DATE OF AMENDMENT: None
3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: December 1, 2000
- C. REMARKS: The subject drug product is manufactured by American Pharmaceutical Partners, Inc. at its manufacturing facility located in Melrose Park, IL in the _____ The _____
- D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments To Be Provided To The Applicant" found at the end of this review. The above deficiencies represent a Fax amendment.


Nrapendra Nath, Ph. D.

12/00



12/12/00

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75-837.doc
Initialed by A. High

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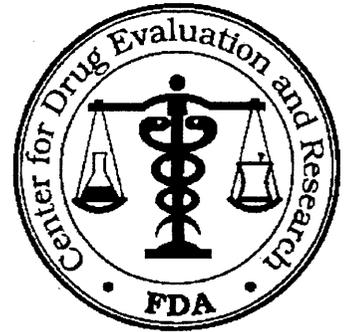
commercial

information

FAX AMENDMENT

ANDA 75-837

DEC 21 2000



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: American Pharmaceutical Partners TEL: (708) 343-6100

ATTN: Tom Stotoff

FAX: (708) 343-4269

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Floxuridine for Injection USP, 500 mg/vial.

Reference is also made to your amendment dated November 4, 2000.

Attached are 2 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

12/20/00 MD

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commercial

information

2

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #2
January 23, 2001

- A. 1. ANDA 75-837
- APPLICANT: American Pharmaceutical Partners, Inc.
2. PRODUCT NAME: Floxuridine for Injection, USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg/vial;
Intra arterial infusion.
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: March 31, 2000
2. DATE OF AMENDMENT: January 15, 2001
Subject of this Review (Received January 17, 2001)
3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: January 23, 2001
- C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated December 21, 2000.
- D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

15/ 1/24/01

Nrapendra Nath, Ph. D.

(CBP) 1/24/01

CC: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75-837a2.doc
Initialed by A. High

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

75-837

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-837

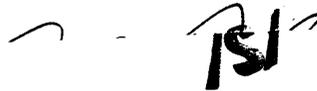
APPLICANT: APP

DRUG PRODUCT: Floxuridine Injection, 500 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

2

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA # 75-837 SPONSOR : American Pharmaceutical
Partners (APP)

DRUG & DOSAGE FORM : Floxuridine Injection

STRENGTH : 500 mg/vial

TYPES OF STUDY: Waiver Request

SUMMARY:

Waiver Request: Granted per 21 CFR Section 320.22(b)(1)

PRIMARY REVIEWER : Lin-Wei Chuang BRANCH : I

INITIAL : *JS!* DATE : 5/23/00

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : *JS!* DATE : 5/23/2000

DIRECTOR
DIVISION OF BIOEQUIVALENCE : Dale Conner, Pharm.D.

INITIAL : *JS!* DATE: 6/1/00

Floxuridine
Injection
500 mg/vial
ANDA #75-837

American Pharmaceutical
Partners, Inc. (APP)
Melrose Park, IL
Submission Date:
March 31, 2000

Reviewer: Lin-Whei Chuang
V:\FIRMSAM\AMERICAN\LTRS&REV\75837W.300

Review of a Waiver Request

Background:

Floxuridine produces the same toxic and antimetabolite effects as does 5-fluorouracil when it is catabolized to 5-fluorouracil after rapid intra-arterial injection. It is indicated for the palliative management of gastrointestinal adenocarcinoma metastatic to the liver.

The reference listed drug (RLD) is FUDR, 500 mg/vial, marketed by Roche (NDA #16929, 12/17/1970).

Review:

The firm is requesting a waiver of the *in-vivo* bioequivalence requirements for the test drug based on 21 CFR 320.22(b)(1).

The comparative formulations of the test and reference drugs are:

<u>Ingredients</u>	Test Drug - Floxuridine for Injection, 500 mg/vial (APP)	RLD- FUDR, 500 mg/vial (Roche)
Floxuridine, USP	500 mg / vial	500 mg / vial

Both test and reference drugs are labeled to be reconstituted with 5 mL of sterile water for injection resulting in a drug concentration of 100 mg/mL, which is further diluted with 5% dextrose or 0.9% sodium chloride for injection to a volume appropriate for the infusion apparatus.

Comments:

1. The test drug meets the criteria for waiver of the *in-vivo* bioequivalence study requirements set forth in 21 CFR 320.22(b)(1):

- a. After reconstitution, the test drug product is a parenteral solution solely for administration by injection.
 - b. It contains the same active and inactive ingredients in the same concentration as Sterile FUDR of Roche Laboratories approved through NDA #16929.
2. The waiver request of the test drug is granted per 21 CFR Section 320.22(b)(1).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by APP demonstrates that its Floxuridine Injection, 500 mg/vial, falls under 21 CFR 320.22 (b)(1). Therefore, the waiver of *in vivo* bioequivalence study requirements for Floxuridine Injection, 500 mg/vial, is granted. The test product, Floxuridine Injection, 500 mg/vial, is deemed bioequivalent to Sterile FUDR marketed by Roche Laboratories.

The firm should be advised of the recommendation.

ISI
5/23/00

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG

ISI
5/23/2000

Concur (_____) ISI
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

Date: 6/1/00

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-837 SPONSOR : American Pharmaceutical
Partners (APP)

DRUG & DOSAGE FORM : Floxuridine Injection

STRENGTH : 500 mg/vial

TYPES OF STUDY: Waiver Request

SUMMARY:

Waiver Request: Granted per 21 CFR Section 320.22(b)(1)

PRIMARY REVIEWER : Lin-Whei Chuang BRANCH : I

INITIAL : _____

LSI

DATE : _____

5/23/00

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : _____

LSI

DATE : _____

5/23/2000

DIRECTOR

DIVISION OF BIOEQUIVALENCE : Dale Conner, Pharm.D.

INITIAL : _____

LSI

DATE: _____

6/1/00

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-837

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-837

FIRM: American Pharmaceutical Partners, Inc (APP)
2045 North Cornell Avenue
Melrose Park, IL 60160

DOSAGE FORM: Injectable

STRENGTH: 500 mg/vial

DRUG: Floxuridine for Injection USP

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities is pending.

BIO STUDY:
Bio status: Acceptable as of 6-1-00.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV is not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Acceptable for approval per T. Watkin's review completed on 11-1-00.

STERILIZATION VALIDATION (IF APPLICABLE):
Micro review: Acceptable per N. Nath review completed on 1-24-01.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):
No bio batch. Bio waiver is requested and granted.

Source of NDS:
DMF # Adequate per review completed on 11-20-00 by this reviewer.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Stability batch is lot # R199-012 and its size is

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Intended production batch size

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

Mujahid L. Shaikh/1/26/01

Review Chemist

Division of Chemistry I

OGD/CDER

V:\firmsam\app\ltrs&rev\75837app.sum

HFD-625/MSmela/1/26/01

/S/ 1/30/01
/S/ 1/30/01

APPEARS THIS WAY
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

-ANDA Number: 75-837

Date of Submission: March 31, 2000

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Floxuridine for Injection USP, 500 mg/vial

Labeling Deficiencies:

1. CONTAINER (500 mg)

- a. Revise _____ to read "Vial stoppers do not contain natural rubber latex".
- b. Delete " _____ "
- c. Revise your storage temperature recommendation so that the Celsius degrees precedes the Fahrenheit degrees.

2. CARTON (1 x 500 mg) - See comments under CONTAINER.

3. INSERT

- a. **DOSAGE AND ADMINISTRATION** (Last paragraph, second sentence) – Revise to read as follows:
...have been published. ¹⁻⁷
- b. **HOW SUPPLIED** – Revise " _____ " to read "Vial stoppers do not contain natural rubber latex."
- c. **PRECAUTIONS (Nursing Mothers)** - Revise " _____ " to read "Floxuridine" in the first and second sentences of this subsection.
- d. **ADVERSE REACTIONS** - Revise " _____ " to read "Floxuridine" in the first sentence of this section and throughout the text as appropriate.
- e. **REFERENCES** – Include the following to appear as reference #7:

- 7. **OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs.**
Am J Hosp Pharm 1986; 43: 1193-1204.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rlid/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

IS/

Wm. Peter Rickman,
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-837

CORRESPONDENCE

January 15, 2001

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773
FAX: 301-827-4337

ARCHIVAL

ANDA ORIG AMENDMENT

FA

Re: **ANDA 75-837**
Floxuridine for Injection, USP
500 mg/vial (Product Code 104507)
Manufacturing Site: Melrose Park, IL

FAX AMENDMENT

Dear Mr. Buehler:

Reference is made to our March 31, 2000 submission of an original Abbreviated New Drug Application (ANDA) for Floxuridine for Injection, USP 500 mg/vial, ANDA # 75-837. Reference is also made to the attached December 21, 2000 FDA FAX Deficiency Letter regarding chemistry and microbiology deficiencies.

American Pharmaceutical Partners, Inc. (APP) is submitting this FAX AMENDMENT in response to each of the comments made in your communication dated December 21, 2000. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

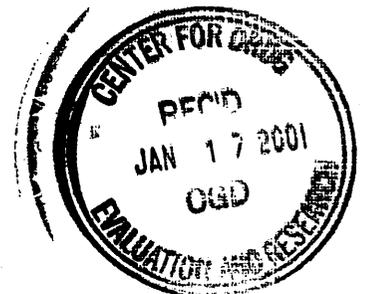
Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at (708) 547-2384 or Mitchall Clark, Vice President, Regulatory Affairs at (708) 547-3618.

Sincerely,



Tom Stothoff
Sr. Regulatory Scientist





ORIG AMENDMENT

N/A/M

November 4, 2000

ARCHIVAL

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 75-837**
Floxuridine for Injection, USP
500 mg/vial (Product Code 104507)
Manufacturing Site: Melrose Park, IL

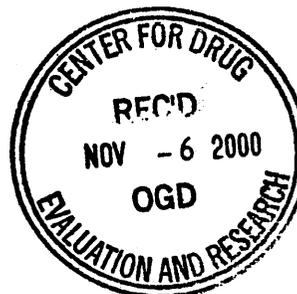
MINOR Amendment to Original ANDA

Dear Mr. Buehler:

Reference is made to our March 31, 2000 submission of an original Abbreviated New Drug Application (ANDA) for Floxuridine for Injection, USP 500 mg/vial, ANDA # 75-837. Reference is also made to the attached October 6, 2000 MINOR Deficiency Letter to this application and to our October 24, 2000 teleconference with M. Smela and M. Dillahunt of the FDA in which APP sought clarification of a couple of the deficiency items.

American Pharmaceutical Partners, Inc. (APP) is submitting this MINOR amendment in response to each of the comments made in your communication dated October 6, 2000. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response. Final Printed Labeling (FPL) is included in this response.

Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.



IS/ 11-8-00

Gary Buehler, Acting Director
Office of Generic Drugs
November 4, 2000
Page 2

If you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at (708) 547-2384 or Mitchall Clark, Vice President, Regulatory Affairs at (708) 547-3618.

Sincerely,



Tom Stothoff
Sr. Regulatory Scientist



APPEARS THIS WAY
ON ORIGINAL

October 11, 2000

NEW CORRESP
NZ

ARCHIVAL

replied
M. Stothoff
10/19/00

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 75-837**
Floxuridine for Injection, USP
500 mg/vial in 5 mL vial (Code 104507)
Manufacturing Site: Melrose Park, IL

INTENT TO FILE AN AMENDMENT

Dear Mr. Buehler:

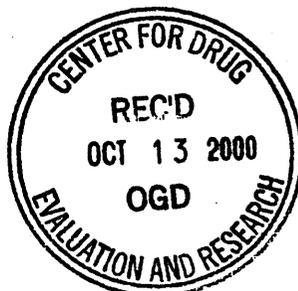
Reference is made to American Pharmaceutical Partners, Inc. (APP) Abbreviated New Drug Application for Floxuridine for Injection, USP (ANDA 75-837). Reference is also made to FDA's MINOR chemistry deficiency letter dated October 6, 2000 regarding Chemistry, Bioequivalence and Labeling Deficiencies. In accordance with 21 CFR 314.120(a)(1), APP is informing you of our **intent to file an amendment** in response to this communication shortly.

Should you have any questions or concerns, please contact the undersigned at (708) 547-2384 or Mitchall Clark, Vice President, Regulatory Affairs at (708) 547-3618.

Sincerely,



Tom Stothoff
Sr. Regulatory Scientist



ISI
10/16/00

August 25, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

ANDA DRUG AMENDMENT
AA

Re: **ANDA 75-837**
Floxuridine for Injection, USP
500 mg/vial in 5 mL vial (Code 104507)
Manufacturing Site: Melrose Park, IL

AMENDMENT TO ORIGINAL ANDA

Dear Mr. Buehler:

Reference is made to our Original Abbreviated New Drug Application submitted March 31, 2000 for Floxuridine for Injection, USP.

Since this application was filed, American Pharmaceutical Partners (APP) has received several common deficiencies on similar ANDAs, and is therefore amending this application to address these concerns.

APP is submitting this amendment to provide a revised Master Batch Record for commercial production of Floxuridine for Injection, USP. The batch record was revised for the following reasons:

- ~~_____~~
- The wording on Page M-2, 1 of 2, was revised to make it clear that a sample will be taken for in-process testing for chemistry (step 4: assay and appearance) and microbiology (step 6: _____ bioburden).

Provided in **Attachment 1** is a copy of the revised Master Batch Record.

- In-Process tests for appearance and _____ bioburden were also added.

Provided in **Attachment 2** is a copy of the revised In-Process Specifications.



Gary Buehler, Acting Director
August 25, 2000
Page 2

In compliance with 21 CFR 314.96(b), a true and complete copy of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

If you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at (708) 547-2384 or Mitchall Clark, Vice President, Regulatory Affairs, at (708) 547-3618.

Sincerely,

A handwritten signature in black ink that reads "Tom Stothoff". The signature is written in a cursive style with a horizontal line through the middle of the letters.

Tom Stothoff
Senior Regulatory Scientist

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-837

American Pharmaceutical Partners, Inc.
Attention: Tom Stothoff
2045 North Cornell Avenue
Melrose Park, IL 60160
|||||

[MAY 3 2000]

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Floxuridine for Injection USP, 500 mg/vial

DATE OF APPLICATION: March 31, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 4, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



March 31, 2000

505 (j) (2) (A) OK
41-181 1/26/00
181

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

**Re: Floxuridine for Injection, USP
500 mg/vial in 5 mL vial (Code 104507)
Manufacturing Site: Melrose Park, IL
Number of Volumes: 5 Volumes**

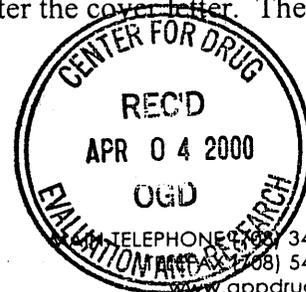
ORIGINAL ANDA

Dear Mr. Buehler:

This Abbreviated New Drug Application is submitted in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Floxuridine for Injection, USP. The reference listed drug is FUDR[®], manufactured by Roche Laboratories, Inc.

American Pharmaceutical Partners, Inc. will manufacture this product in manufacturing facilities located at 2020 Ruby Street, Melrose Park, IL 60160. This application contains all the information required describing the chemistry, manufacturing and control of Floxuridine for Injection, USP 500 mg/vial in a 5 mL vial. This application contains a request for the waiver of *in vivo* bioequivalence studies. **This application also contains microbiology and sterility assurance information, which is provided in Section XXII.**

The application has been formatted according to the information in the Guidance for Industry: Organization of an ANDA, dated February 1999. An Executive Summary explaining the organization of this application is included after the cover letter. The application consists of 5 volumes.



March 31, 2000
Page 2

American Pharmaceutical Partners Inc. is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the ANDA, and a technical review copy (in a red folder) which contains all of the information in the archival copy with the exception of the bioequivalence section (Section VI). Three copies of the analytical methods validation section are included in red folders. Four copies of the draft labeling are included in both the archival and the review copies. A separate copy of the bioequivalence section is provided in an orange folder. The bioequivalence section consists of a request for a waiver from the need to conduct a bioequivalence study.

Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this Abbreviated New Drug Application is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606. We certify that the Field Copy is a true and complete copy of this Abbreviated New Drug Application.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at (708) 547-2384 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,



Tom Stothoff
Senior Regulatory Scientist

**APPEARS THIS WAY
ON ORIGINAL**

April 12, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

NEW CORRESP

DMF # noted.
NAT.
4/24/00

Re: **Floxuridine for Injection, USP**
500 mg/vial in 5 mL vial (Code 104507)
Manufacturing Site: Melrose Park, IL

AMENDMENT TO ORIGINAL ANDA

ISI

Dear Mr. Buehler:

Reference is made to our Original Abbreviated New Drug Application submitted March 31, 2000 for Floxuridine for Injection, USP. Reference is also made to the attached FDA April 4, 2000 correspondence to _____ is the _____ and American Pharmaceutical Partners, Inc. (APP) is the U.S. Agent for _____

At the time APP submitted the original ANDA, the DMF number was yet to be assigned. This amendment provides an updated DMF authorization letter which includes the recently assigned DMF number (DMF # _____) s Type II Drug Master File.

In compliance with 21 CFR 314.96(b), a true and complete copy of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

If you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at (708) 547-2384 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,



Tom Stothoff
Senior Regulatory Scientist

